PEDIATRIC DR-TB MENINGITIS: CASE-BASED DISCUSSION

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Learning points

• The diagnosis of DR-TB meningitis in children
• Strategies to manage complications and reduce mortality
• Anti-TB drug regimen selection and empiric therapy
Pediatric DR-TB meningitis is an underappreciated problem

- Estimated 33,000 incident cases of childhood MDR-TB annually
- As many as 1-3% of pediatric cases present with meningitis.
- More common manifestation in children than adults

Pediatric TBM is bad and drug resistance makes it even worse

- Near complete mortality in untreated disease
- 80% of children with advanced disease will have permanent neurologic sequelae despite treatment.
- Drug resistance associated with poor outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Characteristics in Model</th>
<th>Variable</th>
<th>Number in Analysis</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavorable outcome</td>
<td>Age</td>
<td>Isoniazid mono-resistant</td>
<td>122</td>
<td>0.22</td>
<td>0.03–1.87</td>
<td>0.17</td>
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<tr>
<td></td>
<td></td>
<td>Rifampin mono-resistant</td>
<td>122'</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td>Multidrug-resistant</td>
<td>122</td>
<td>12.4</td>
<td>1.17–132.3</td>
<td>0.037</td>
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<tr>
<td>Mortality</td>
<td>HIV status</td>
<td>Isoniazid mono-resistant</td>
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<td>6.17</td>
<td>0.92–41.3</td>
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<tr>
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<td>Rifampin mono-resistant</td>
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<tr>
<td></td>
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<td>Multidrug-resistant</td>
<td>88</td>
<td>63.9</td>
<td>4.84–843.2</td>
<td>0.002</td>
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</tbody>
</table>

Outcomes in pediatric MDR-TB meningitis are poor

- Mortality 87.5%
- Delay in diagnosis
- Low rates of contact tracing
- Low rates of steroid use

Georgia has a high burden of MDR-TB

- TB incidence – 116 cases per 100,000
- TB prevalence – 158 cases per 100,000

- MDR TB prevalence:
  - 11% among new cases
  - 38% previously treated cases
Patient 1 – History of present illness

- 9-year-old girl living in a former Soviet Republic with a high incidence of MDR-TB.
- No past medical history; BCG vaccinated at birth.
- Lives with her mother, who is well. Father has MDR-TB.
- Developed fever, fatigue and severe, persistent headaches over a two week period.
Patient 1 - Physical and laboratory examination

- **Weight:** 22 kg
- **Temperature:** > 38°C
- **Neurologic exam:** delirious, neck with limited range of flexion and extension, photophobia
- **Creatinine:** 0.6 mg/dl
- **AST:** 22 IU/L
- **ALT:** 18 IU/L
- **HIV serology:** unknown, but presumed negative
Patient 1 – CSF examination

- **Cell count:** 400 WBC/ml3 (90% lymphocytes)
- **Protein:** 0.66 mg/dl (normal 15-60 mg/dl)

- **CSF microscopy:** AFB negative
- **CSF culture:** positive

**Drug susceptibility testing:**

- Resistant – INH, Rif, S, Ofx, Eth
- Sensitive – Km, Cm
Patient 1 – Treatment regimen

- Pyrazinamide 600mg PO daily
- Capreomycin 0.6 g IM daily
- Levofloxacin 250 mg PO daily
- Cycloserine 250 mg PO daily
- Prothionamide 250mg PO daily
- PAS 4.0 g PO daily
- Amoxicillin/clavulanate 1 g PO daily
- Clarithromycin 1 g PO daily
- Clofazimine 250mg PO daily
Patient 1 – Persistent symptoms despite treatment

- Patient continued to complain of fatigue one month into treatment
- Physical exam revealed persistent neurologic signs.
- Repeat lumbar puncture:
  - CSF cell counts increased to 824 cells/mm³
  - Protein increased to 0.99 mg/dl
Patient 1 – Imaging while on treatment

- Head MRI at month two of treatment showed obstructive hydrocephalus, paraventricular swelling and inflammation of the inner capsule.

- Dexamethasone was subsequently started in an attempt to decrease inflammation.
Patient 1 – Further worsening

• Clinical condition did not improve. The patient developed seizures, nausea and vomiting.

• Repeat MRI showed increased hydrocephaly.

• Subsequently underwent placement of an extra-ventricular drain by neurosurgery with good results.
  – Seizures and headaches resolved.
  – Nausea and vomiting continued.
Patient 1 – Outcome

- Regimen was modified: capreomycin, levofloxacin, cycloserine, prothionamide
- Subsequently gained weight, temperature normalized, headache did not recur.
- Completed 20 months of treatment.
Delay in diagnosis

• Delay in diagnosis is common, leading to increased morbidity and mortality.
• Highest risk: very young patients, patients with co-existing illness and those from non-TB endemic regions.
• Single most important factor in predicting outcome.
Early stage pediatric TBM is difficult to recognize

- Peak incidence between 2 and 4 years of age
- Presents with nonspecific symptoms of ill health
  - poor weight gain
  - low-grade fever
  - listlessness
- Classic neurologic signs are usually seen only in advanced disease

Classic CSF finding of TBM

- Low glucose: less than 45 mg/dL in 80 percent of cases
- High protein: ranges from 100 to 500 mg/dL in most patients; however, patients with subarachnoid block may show extremely high levels (2 to 6 g/dL)
- Lymphocytic pleocytosis: between 100 and 500 cells/microL

CSF microscopy

- Ziehl-Neelsen microscopy staining of CSF is the most widely applied rapid diagnostic technique for TBM.
- Sensitivity usually below 20%
- Analysis of a large volume (7 ml) of CSF and examination time of 30 minutes per slide improves sensitivity
CSF culture

• Sensitivity of almost 60%
• Not feasible to rule in or rule out disease because test take weeks to return positive results.
• Requires robust laboratory facilities
Sensitivity of Xpert for TBM compared to other diagnostic tests

Xpert sensitivity across sample types

Pathogenesis of TBM

Third Ventricle

Fourth Ventricle

Cisterns
Complications of TBM

• Tuberculous hydrocephalus and raised intracranial pressure
• Tuberculosis cerebrovascular disease
• Hyponatremia
• TB mass lesions
• TB-immune reconstitution inflammatory syndrome
Grading of TBM

• Grade 1: Fully conscious, rational and no neurologic signs
• Grade 2: Confused but not comatose; neurologic signs limited to hemiparesis or single cranial nerve palsy
• Grade 3: comatose or stuporous; multiple cranial nerve palsies or complete hemiplegia or paraplegia
Low cost interventions to manage complications of pediatric TBM

- Control of hyponatremia and cerebral salt wasting
- Intravascular volume support
- Elevation of the head of bed
- Acetazolamide and furosemide for communicating hydrocephalus

Systemic steroids for anti-inflammatory therapy

• Cochrane meta analysis of corticosteroids in 1140 HIV uninfected participants.
  – Reduced the risk of death (relative risk = 0.78, 95% CI: 0.67 – 0.91)
  – Reduced risk of disabling neurological deficit (relative risk = 0.82, 95% CI 0.70 – 0.97)

• Prednisone: 2 to 4 mg/kg per day (max 60 mg/day) for the first month of treatment, then wean.
• Dexamethasone can be used as an alternative.
Thalidomide can be effective against tuberculomas

- Thalidomide moderates the production of TNF-alpha, which can reduce abscess size.

- Dose 3-5 mg/kg/day orally in children who develop life threatening TB mass lesions despite corticosteroids.
Ventricular drains

• To decompress the ventricular system and reduce intracranial pressure.
• Requires neurosurgical placement
• Serial lumbar puncture as a temporizing measure if neurosurgery isn’t available
Patient 2 – History of present illness

• 15-year-old girl living in a former Soviet Republic with a high incidence of MDR-TB.
• No past medical history; BCG vaccinated at birth. HIV negative.
• No close contact with an active case of DR-TB.
• Developed fever, fatigue and severe, persistent headaches over a one week period.
Patient 2 - Physical and laboratory examination

- **Weight:** 50 kg
- **Temperature:** $> 38^\circ C$
- **Neurologic exam:** neck with limited range of flexion and extension, positive Kerning sign, remainder of physical exam not documented
- **Chest x-ray:** normal
Patient 2 – CSF examination

- **Cell count**: 580 WBC/ml³ (90% lymphocytes)
- **Protein**: 0.63 mg/dl (normal 15-60 mg/dl)

- **CSF microscopy**: AFB negative
- **CSF culture**: negative
Patient 2 – Treatment regimen

- Isoniazid 300 mg PO daily
- Rifampicin 600 mg PO daily
- Pyrazinamide 1600 mg PO daily
- Ethambutol 1200 mg PO daily
Patient 2 – Failure to improve

- Condition did not improve on first-line TB treatment
- Clinical picture was concerning for MDR-TB
- Patient was hospitalized and her treatment regimen was modified to include first-line anti-TB drugs and empiric MDR-TB therapy:
  - isoniazid, rifampicin, ethambutol, pyrazinamide, capreomycin, ofloxacin, cycloserine and PAS.
Patient 2 – Outcome

• Patient’s temperature normalized and she gained weight.
• Patient was discharged from the hospital and was treated as an outpatient.
• Completed 20 months of treatment
Contact tracing

• Critical in children with TB meningitis, especially for those whose diagnosis is not confirmed microbiologically.

• Consider Xpert MTB/RIF testing to quickly identify MDR-TB in the contact, thereby helping to guide therapy in the index pediatric patient.
Empiric therapy

• The *a priori* risk for MDR-TB should be assessed.

• Low risk patients without microbiologic diagnosis should be initiated on empiric first-line therapy and then switched to MDR-TB therapy after failing to respond in the first month of therapy.

• The threshold for switching regimens should be relatively low in patients in highly endemic MDR-TB settings who fail to respond to first-line drugs.
Dosing and CNS penetration

• The MDR-TB regimen should include an injectable, a quinolone and at least other two likely active second line drugs plus pyrazinamide.
• Controlled trials to determine the optimal drug regimen and treatment duration for TBM have not been conducted.
• There is no good data on CNS penetration.
Conclusions I

• Pediatric DR-TB is an unrecognized problem with fatal consequences for children
• Poor outcomes mainly associated with delays in diagnosis
• Need high index of suspicion and look for isolated vomiting, headache, fatigue and decreased play
• Contact history is key in making the diagnosis, but need to ask additional questions about contacts to assess risks
Conclusions II

• NAAT (i.e. Xpert) are preferred diagnostic test under program conditions, although culture should also be done if possible

• Principles follow management of pulmonary MDRTB in children, but may need adjuvant steroids, drainage/EVD; thalidomide may have a possible role in cases complicated by brain abscess

• Empiric MDR-TB therapy when risk of disease is moderate
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